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Instantaneous limits of reversible chemical reactions in presence of macroscopic convection ☆

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Abstract

Chemically reacting systems frequently involve fast reversible reactions, additional slow reactions as well as mass transport due to macroscopic convection. In this situation, the passage to infinite reaction speed is a means to reduce the complexity of the reaction kinetics and to avoid the need for explicit values of the rate constants. Thereby the large stiffness of the original system of differential equations is also removed.

In the present paper this instantaneous reaction limit is studied for systems with independent fast reversible reactions, where the rate functions are given by mass-action kinetics. Under realistic assumptions the limiting dynamical system is derived and convergence of the solutions is obtained as the rate constants tend to infinity. The proof is based on Lyapunov functions techniques and exploits the structure of rate functions that results from mass-action kinetics.

This approach is complementary to the quasi-steady-state approximation which is often applied in chemical engineering. The differences are illustrated by means of a classical enzyme–substrate reaction scheme.

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1. Introduction

Chemically reacting systems almost always involve elementary reaction steps that are reversible and fast. Apart from additional slow reactions that might occur, mass transport will also be important especially if reactions take place in a fluid phase. If the fluid phase is ideally mixed this leads to mathematical models of the type

$$\dot{c}(t) = f(c(t)) + kr(c(t)), \tag{1}$$

where $c = (c_1, \dots, c_n)$ denotes the vector of concentrations of all chemical species involved, f models additional slow reactions as well as mass transport due to macroscopic convection, r corresponds to the kinetics of the fast reversible reactions and $k > 0$ is a large parameter.

If the reaction mechanism is considered on the level of elementary reactions, then the rates of the elementary steps are given by *mass-action kinetics* within good accuracy. The basic idea behind is that two atoms or molecules A and B need to interact in a kind of collision in order to react with each other, and the rate of collisions is proportional to the probability that A and B are at the same position. If these events are stochastically independent the rate will be proportional to the product of these probabilities, hence to the product of the concentrations of the corresponding species. Consequently, in case of a reaction

$$A + B \to P,$$

mass-action kinetics leads to the *reaction rate* $r = k\, c_A c_B$ with a *rate constant* $k > 0$ which is a measure of the reaction speed. For the reversible reaction

$$A + B \rightleftharpoons P$$

the same approach yields $r = kc_A c_B - k' c_P = k(c_A c_B - \kappa c_P)$ with the *equilibrium constant* $\kappa = k'/k > 0$; see [5] for further details. Let us note that for a complex reaction $A + B \rightleftharpoons P$, i.e. a reaction that takes place in more than one elementary step, the same type of reaction rate may also be realistic. This depends on the structure and speed of the elementary steps. Therefore, mass-action kinetics is widely applied in practice.

For concrete reversible reactions the equilibrium constants can often be obtained from the literature or by means of measurements, while the individual rate constants are usually unknown especially for fast reactions. On the other side, it is reasonable to expect that during the evolution according to (1) the chemical composition $c(t)$ will be close to the manifold on which all fast reversible reactions are in equilibrium, driven by the additional "forcing" $f(c)$. Hence a natural question is whether solutions of (1) converge to the solution of an associated limit problem if k tends to infinity. In the present paper we obtain the system of differential equations corresponding to the limiting case of instantaneous reversible reactions. The main result (Theorem 2) yields the convergence of the solutions of (1) to the solution of this limit problem under realistic assumptions on f, given that the rates of all fast reversible reactions are governed by mass-action kinetics.

The analysis of reaction networks given here relies on the decomposition into fast reversible and slow reactions, a viewpoint that is also taken in the related paper [7] and in Chapter 12 of [12]. A complementary approach underlies the quasi-steady-state approximation (QSSA) which is often applied in chemical engineering. Within this approach the species are decomposed into fast and slow variables, where the fast variables correspond to intermediates and are assumed to be in steady state. More details about QSSA can be found in [4,5] and especially in [10].

2. Systems of independent reversible reactions

We start with a compilation of basic facts concerning the dynamics of systems of independent reversible reactions (with finite reaction speed) under the assumption of mass-action kinetics, which is given in Theorem 1. Although these facts are essentially known, we include a short proof adapted to the special situation considered here, since most of the arguments will also be important in the study of the instantaneous reaction limit.

Suppose that m reversible reactions

$$\alpha_{j,1}C_1 + \cdots + \alpha_{j,n}C_n \rightleftharpoons \beta_{j,1}C_1 + \cdots + \beta_{j,n}C_n \quad (j = 1, \ldots, m)$$

take place inside a continuously stirred isolated vessel, involving chemical species $C_1, \ldots, C_n$. Here $\alpha_j = (\alpha_{j,1}, \ldots, \alpha_{j,n})$ and $\beta_j = (\beta_{j,1}, \ldots, \beta_{j,n})$ with $\alpha_{j,i}, \beta_{j,i} \in \mathbb{N}_0$ are the *stoichiometric vectors* corresponding to the jth reaction. We always assume independence of the reactions, which means that $\{v_1, \ldots, v_m\}$ with $v_j \coloneqq \beta_j - \alpha_j$ is a linearly independent subset of $\mathbb{R}^n$. Equivalently, the *stoichiometric matrix* $N = (v_1^T, \ldots, v_n^T)$ satisfies $\ker(N) = \{0\}$. On the basis of mass-action kinetics the rate function of the jth reaction is given by

$$r_j(c) = k_j(c^{\alpha_j} - \kappa_j c^{\beta_j}) \quad \text{with } k_j, \kappa_j > 0,$$

where the abbreviation $c^x = \prod_{i=1}^n c_i^{x_i}$ for $c \in \mathbb{R}_+^n$ and $x \in \mathbb{N}_0^n$ (with $0^0 \coloneqq 1$) is used.

In addition to the abbreviation c^x, the following condensed notation will be employed throughout this paper: $c \gg 0$ is short for $c_i > 0$ for all i, and

$$g(c) \coloneqq (g(c_1), \ldots, g(c_n)) \text{ for } c \gg 0 \text{ where } g : (0, \infty) \to \mathbb{R},$$

$$h(c, \bar{c}) \coloneqq (h(c_1, \bar{c}_1), \ldots, h(c_n, \bar{c}_n)) \text{ for } c, \bar{c} \gg 0 \text{ where } h : (0, \infty)^2 \to \mathbb{R}.$$

So, for example, $e^c = (e^{c_1}, \ldots, e^{c_n})$, $c/\bar{c} = (c_1/\bar{c}_1, \ldots, c_n/\bar{c}_n)$ and $c \cdot \bar{c} = (c_1\bar{c}_1, \ldots, c_n\bar{c}_n)$.

In the situation described above, mass balance for all involved species shows that the time evolution of the composition vector $c = (c_1, \ldots, c_n)$ is governed by the initial value problem

$$\dot{c} = \sum_{j=1}^{m} v_j r_j(c) \text{ on } \mathbb{R}_+, \quad c(0) = c_0. \tag{2}$$

Since the right-hand side has its values in the *stoichiometric space* $S = \mathrm{Im}(N)$, every solution remains inside the so-called *stoichiometric class* $c_0 + S$ determined by its initial value c_0. Below we will sometimes use the dual formulation of this fact: if E denotes an $(n-m) \times n$-matrix of full rank such that $\ker(E) = S$, then $Ec(t) \equiv Ec_0$ for every solution of (2). In the sequel the letter E will always stand for such a matrix. Evidently $\mathrm{Im}(E^T) = S^\perp$ then, and every $e \in S^\perp \setminus \{0\}$ corresponds to a "conservation law" of the system of chemical reactions. The system is said to be *conservative* if there is $e \in S^\perp$ such that $e \gg 0$. In particular, the latter holds if all involved species have an atomic structure and the total number of atoms (of each type) is conserved under chemical reactions; see Chapter 3 in [4]. The subsequent example serves to illustrate the above introduced notions. Consider the system of two concurrent reversible reactions

$$C_1 + C_2 \rightleftharpoons C_3, \quad 2C_1 \rightleftharpoons C_4.$$

The dynamics of this system is described by (2), where $c = (c_1, c_2, c_3, c_4)$,

$$\begin{matrix} v_1 = (-1, -1, 1, 0), & r_1(c) = k_1(c_1 c_2 - \kappa_1 c_3), \\ v_2 = (-2, 0, 0, 1), & r_2(c) = k_2(c_1^2 - \kappa_2 c_4), \end{matrix} \qquad N = \begin{pmatrix} -1 & -2 \\ -1 & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

A possible choice for E is given by

$$E = \begin{pmatrix} 1 & 0 & 1 & 2 \\ 0 & 1 & 1 & 0 \end{pmatrix}.$$

This system of chemical reactions is conservative, since $0 \ll e = (1,\ 1,\ 2,\ 2) \in S^\perp$.

In the analysis of (2) we have to care about nonnegativity of solutions, since these constraints are imposed by the underlying physics. For this purpose it is helpful to use the well-known characterization of flow invariance by means of subtangential conditions. In the sequel, we shall apply the following result (see e.g. [1, Theorem 16.5]), where $\rho(x, D)$ denotes the distance of a point $x \in \mathbb{R}^n$ to the set $D \subset \mathbb{R}^n$.

Lemma 1. *Let $D \subset \mathbb{R}^n$ be closed and $F : D \to \mathbb{R}^n$ be locally Lipschitz continuous such that*

$$\lim_{h \to 0+} \frac{1}{h} \rho(c + hF(c), D) = 0 \quad \text{on } D. \tag{3}$$

Then

$$\dot{c} = F(c) \ \ on \quad \mathbb{R}_+, \quad c(0) = c_0$$

has a unique local solution for every $c_0 \in D$.

Specialized to $D = \mathbb{R}^n_+$, the subtangential condition (3) reduces to

$$F_i(c) \geqslant 0 \quad \text{for every } c \in \mathbb{R}^n_+ \text{ such that } c_i = 0.$$

Recall that such $F : \mathbb{R}^n_+ \to \mathbb{R}^n$ is called *quasi-positive*.

The subsequent result provides basic facts about the manifold of stationary points of system (2) and about the asymptotic behavior of its solutions.

Theorem 1. *Let* $\alpha_j, \beta_j \in \mathbb{N}^n_0$ *for* $j = 1, \dots, m$ *be such that* $\{v_1, \dots, v_m\}$ *with* $v_j = \beta_j - \alpha_j$ *is a linearly independent subset of* $\mathbb{R}^n$. *Let* $k_j, \kappa_j > 0$ *and* $r_j(c) = k_j(c^{\alpha_j} - \kappa_j c^{\beta_j})$ *for* $j = 1, \dots, m$. *Then the following holds*:

(a) *For every* $c_0 \gg 0$ *there is a unique equilibrium* $\bar{c} \gg 0$ *of* (2) *within the stoichiometric class* $c_0 + S$. *If* $c^* \gg 0$ *is any equilibrium, there is* $x \in S^\perp$ *such that* $\bar{c} = c^* \cdot e^x$.
(b) *For every* $c_0 \gg 0$ *there is a unique solution of* (2). *This solution is strictly positive and exists globally.*
(c) *Given* $c_0 \gg 0$, *the solution* $c(\cdot; c_0)$ *of* (2) *satisfies* $c(t; c_0) \to \bar{c}$ *as* $t \to \infty$, *where* $\bar{c}$ *is the strictly positive equilibrium in the stoichiometric class* $c_0 + S$. *In addition, there is* $\eta = \eta(c_0) > 0$ *such that* $c_i(t; c_0) \geqslant \eta$ *on* $\mathbb{R}_+$ *for* $i = 1, \dots, n$.

Proof. (a) Notice first that $c \gg 0$ is an equilibrium of (2) iff

$$c^{v_j} = 1/\kappa_j \quad \text{for all } j = 1, \dots, m.$$

Indeed, since $v_1, \dots, v_m$ are linearly independent, a composition $c \gg 0$ is a stationary point of (2) iff $r_j(c) = 0$ for all $j = 1, \dots, m$, i.e. iff $c^{\alpha_j} = \kappa_j c^{\beta_j}$ for all j.

Therefore, $c := e^x$ is a strictly positive equilibrium if x is a solution of $N^T x = y$ with $y = (-\ln \kappa_1, \dots, -\ln \kappa_m)$, and such a solution exists due to $\mathrm{Im}(N^T) = (\ker(N))^\perp = \{0\}^\perp = \mathbb{R}^n$. Moreover, given an arbitrary stationary solution $c \gg 0$, the set of all equilibria is given as $\{c \cdot e^x \colon x \in S^\perp\}$. If c, c^* are equilibria in the class $c_0 + S$, then $\ln c - \ln c^* \in S^\perp$ implies

$$c - c^* \perp \ln c - \ln c^* \quad \Leftrightarrow \quad \sum_{i=1}^n (c_i - c_i^*)(\ln c_i - \ln c_i^*) = 0.$$

Hence $c = c^*$, since the logarithm is strictly increasing. Consequently, there is at most one equilibrium in every stoichiometric class.

To prove existence within the class $c_0 + S$, fix any equilibrium $c \gg 0$. It suffices to find $x \in S^\perp$ such that $c \cdot e^x - c_0 \in S$. Define $\phi : \mathbb{R}^n \to \mathbb{R}$ by $\phi(x) = \langle c, e^x \rangle - \langle c_0, x \rangle$.

Then $\nabla\phi(x) = c\cdot e^x - c_0$ and $\phi''(x) = \mathrm{diag}(c_i e^{x_i})$ is positive definite, hence ϕ is strictly convex. Consider the set

$$C = \{x \in S^\perp:\ \phi(x) \leqslant \phi(0)\}.$$

Evidently C is closed convex with $0 \in C$. To show that C is also bounded, fix $x \in S^\perp$ with $|x| = 1$ and consider $\phi(sx)$ as a function of $s \in \mathbb{R}_+$. Evidently $\phi(sx) = \sum_{i=1}^n \varphi_i(s)$ with $\varphi_i(s) = c_i e^{sx_i} - c_{0,i} s x_i$. Given $a, b > 0$, it is easy to check that $\varphi(r) = ae^r - br$ is strictly convex with $\varphi(r) \geqslant b(1 - \ln b/a)$ on $\mathbb{R}$. Hence $\phi(sx) \leqslant \phi(0) = |c|_1$ implies

$$\varphi_i(s) \leqslant |c|_1 + (n-1)M \quad \text{with } M = \max_{k=1,\dots,n} c_{0,k}\left|1 - \ln\frac{c_{0,k}}{c_k}\right|.$$

Choose $i \in \{1, \dots, n\}$ such that $|x_i| \geqslant 1/n$. If $x_i > 0$ then

$$\varphi_i(s) \geqslant c_i\left(1 + sx_i + \frac{1}{2}s^2 x_i^2\right) - c_{0,i} s x_i \geqslant c_i - |c_i - c_{0,i}| s + c_i \frac{s^2}{2n^2},$$

hence $sx \in C$ implies

$$c_i - |c_i - c_{0,i}| s + c_i \frac{s^2}{2n^2} \leqslant |c|_1 + (n-1)M$$

and therefore $s \leqslant \rho$ for some $\rho = \rho(c_0, c) > 0$, which does not depend on the choice of x above; in case $x_i < 0$ the same conclusion follows from $\varphi_i(s) \geqslant c_{0,i} s/n$. Hence there is $\rho = \rho(c_0, c) > 0$ such that $x \in C$ implies $|x| \leqslant \rho$, i.e. C is bounded, thus compact. Consequently, there is $x \in C$ such that $\phi(x) \leqslant \phi(z)$ for all $z \in C$. This implies $\langle \nabla\phi(x), v\rangle = 0$ for all $v \in S^\perp$, and therefore $\nabla\phi(x) = c\cdot e^x - c_0 \in S^{\perp\perp} = S$.

(b) To obtain the second assertion observe that the right-hand side in (2) is only defined on $\mathbb{R}^n_+$ where it is locally Lipschitz continuous. We claim that $g(c) = \sum_{j=1}^m v_j r_j(c)$ is quasi-positive. To see this, write $g_i(c)$ as

$$g_i(c) = \sum_{j: v_{j,i} < 0} v_{j,i} r_j(c) + \sum_{j: v_{j,i} > 0} v_{j,i} r_j(c)$$

and notice that for instance $v_{j,i} < 0$ and $c_i = 0$ imply $c^{\alpha_j} = 0$ since $\alpha_{j,i} > 0$. Hence

$$v_{j,i} r_j(c) = |v_{j,i}| k_j \kappa_j c^{\beta_j} \geqslant 0$$

in this case. Consequently $\dot c = g(c)$ and therefore (2) has a unique local solution which stays nonnegative by Lemma 1. Let $c(\cdot)$ denote this solution and let $[0, T)$ be its maximal interval of existence. Due to the above arguments concerning the structure of $g_i(c)$ and the fact that $\alpha_{j,i}, \beta_{j,i} \in \mathbb{N}_0$, it is easy to see that

$$\dot c_i = -\varphi_i(t) c_i + \psi_i(t) \text{ on } [0, T) \quad \text{with continuous } \varphi_i, \psi_i \geqslant 0.$$

By the variation of constants formula it follows that

$$c_i(t) = c_{0,i} \exp\left(-\int_0^t \varphi_i(s)\, ds\right) + \int_0^t \exp\left(-\int_s^t \varphi_i(\tau)\, d\tau\right)\psi_i(s)\, ds > 0 \text{ on } [0, T).$$

It remains to prove global existence which holds if $c(\cdot)$ is bounded on bounded intervals. For this purpose let $\bar{c} \geqslant 0$ be the stationary solution of (2) in the class $c_0 + S$, which exists due to part (a) of this proof, and define $V : (0, \infty)^n \to \mathbb{R}$ by

$$V(c) = \sum_{i=1}^{n} c_i(\ln c_i - \ln \bar{c}_i) - (c_i - \bar{c}_i). \tag{4}$$

Evidently, V is continuously differentiable with $0 \leqslant V(c) \to \infty$ if $c_i \to \infty$ for some i. We claim that V is a Lyapunov function for (2). Indeed, $\nabla V(c) = \ln(c/\bar{c})$ and therefore

$$\langle \nabla V(c), g(c) \rangle = \sum_{i=1}^{n} \sum_{j=1}^{m} v_{j,i} \ln \frac{c_i}{\bar{c}_i}\, r_j(c) = \sum_{j=1}^{m} k_j \ln \frac{c^{v_j}}{\bar{c}^{v_j}}\, (c^{\alpha_j} - \kappa_j c^{\beta_j}).$$

Due to $\bar{c}^{v_j} = 1/\kappa_j$, this implies

$$\langle \nabla V(c), g(c) \rangle = -\sum_{j=1}^{m} k_j c^{\alpha_j} \left[\left(\frac{c}{\bar{c}}\right)^{v_j} - 1\right] \ln\left(\frac{c}{\bar{c}}\right)^{v_j} \leqslant 0. \tag{5}$$

Consequently $V(c(t)) \leqslant V(c_0)$, hence $c(\cdot)$ is bounded on $[0, T)$. Therefore, the unique solution $c(\cdot)$ exists globally and is bounded on $\mathbb{R}_+$.

(c) By the preceding step, all semiorbits are relatively compact. Hence $\rho(c(t), M) \to 0$ as $t \to \infty$ by LaSalle's invariance principle (see e.g. [1, Theorem 18.3]), where $\rho(c, M)$ denotes the distance from c to the set

$$M = \{c^* \in \mathbb{R}_+^n : \; V(c(\cdot; c^*)) \equiv V(c^*)\}.$$

Due to (5) and the fact that $(x-1)\ln x \geqslant \frac{(x-1)^2}{x+1}$ for all $x > 0$, which follows by the mean value theorem, we obtain

$$\langle \nabla V(c), g(c) \rangle \leqslant -\sum_{j=1}^{m} k_j \frac{(c^{\alpha_j} - \kappa_j c^{\beta_j})^2}{c^{\alpha_j} + \kappa_j c^{\beta_j}}. \tag{6}$$

Since the solution $c(\cdot)$ of (2) is globally bounded, this yields

$$\langle \nabla V(c), g(c) \rangle \leqslant -\omega \sum_{j=1}^{m} \frac{1}{k_j} r_j(c)^2 \text{ with some } \omega > 0.$$

Thus $c^* \in M$ means $r_j(c^*) = 0$ for all $j = 1, \dots, m$, i.e. M consists of equilibria. On the other hand, the solution $c(\cdot; c_0)$ of (2) with initial value c_0 stays inside $c_0 + S$, since

$$Ec(t) = Ec_0 + \int_0^T Eg(c(s))\, ds = Ec_0 \quad \text{for all } t \geqslant 0,$$

recall that E denotes a matrix composed of conservation laws. Consequently,

$$\{c^* : c^* = \lim_{k \to \infty} c(t_k; c_0) \text{ for some } t_k \to \infty\} \subset M \cap (c_0 + S) = \{\bar{c}\},$$

hence $c(t; c_0) \to \bar{c}$ as $t \to \infty$. The other assertion in (c) is obvious, since $c_i(t) \geqslant \frac{1}{2} \min_l \bar{c}_l$ on $[T, \infty)$ with some $T > 0$, and $c(\cdot)$ is continuous on $[0, T]$ with $c(t) \gg 0$ by (b). □

Parts (a) and (c) of Theorem 1 are essentially contained in [8]. The proof of part (a) above is based on arguments from [6], where existence of a unique equilibrium in each stoichiometric class is obtained for considerably more general systems of chemical reactions with mass-action kinetics. The argument given here to obtain strict positivity of solutions is taken from [11].

3. Instantaneous limit of reversible reactions

Suppose that a system of slow and fast reactions is performed inside an ideally mixed fluid phase with macroscopic convection, where the fast reactions are reversible and governed by mass-action kinetics. Since we are interested in the limiting case of instantaneous reactions, we study the family of initial value problems

$$\dot{c}^k = f(c^k) + kN\Lambda R(c^k) \quad \text{on } \mathbb{R}_+, \quad c^k(0) = c_0 \tag{7}$$

with a (large) parameter $k \geqslant 0$, and consider the singular limit as $k \to \infty$. Here $N = (v_1^T, \dots, v_m^T)$, $\Lambda = \mathrm{diag}(\lambda_1, \dots \lambda_m)$ with $\lambda_j \in (0, 1]$ and $R_j(c) = c^{\alpha_j} - \kappa_j c^{\beta_j}$ for $j = 1, \dots, m$. The particular formulation with $k\lambda_j$ instead of k_j, takes care of the fact that the ratios k_j/k_l of the rate constants have to remain fixed as $k_j \to \infty$.

To see what are realistic conditions for f, recall that f splits into $g + h$ where g refers to macroscopic convection and h corresponds to additional slow reactions. As an example, if the reactions are performed inside a *continuous stirred tank reactor* (CSTR), then g is given by $g(c) = (1/\tau)(c^f - c)$, where $\tau > 0$ is the so-called holding time of the CSTR, and $c^f \in \mathbb{R}_+^n$ denotes the vector of feed concentrations. Assuming mass-action kinetics for the slow reactions as well, the term h is given by

$$h(c) = \sum_{j=m+1}^{N} k_j(\beta_j - \alpha_j)(c^{\alpha_j} - \kappa_j c^{\beta_j}) \quad \text{with } k_j > 0, \kappa_j \geqslant 0,$$

where $\kappa_j = 0$ if the jth reaction is irreversible. While the concrete structure of g and h is not so important here, it follows that

$$f : \mathbb{R}^n_+ \to \mathbb{R}^n \text{ is locally Lipschitz and quasi-positive,} \tag{8}$$

remember the proof of Theorem 1(b).

Under the natural assumption that the system of chemical reactions is conservative there exists $e \geqslant 0$ such that $\langle e, \beta_j - \alpha_j \rangle = 0$ for all $j = 1, \dots, N$. Therefore, since g has linear growth, another reasonable assumption on f is

$$\langle e, f(c) \rangle \leqslant a(1 + |c|_1) \text{ on } \mathbb{R}^n_+ \text{ with } a \geqslant 0 \text{ and } 0 \ll e \in S^\perp, \tag{9}$$

where $|c|_1$ denotes the l^1-norm of c.

The following result establishes convergence of the solutions $c^k(\cdot)$ of (7) to the solution $c^\infty(\cdot)$ of the limiting equation

$$\dot{c}^\infty = f(c^\infty) - N[R'(c^\infty)N]^{-1} R'(c^\infty) f(c^\infty) \quad \text{on } \mathbb{R}_+, \quad c^\infty(0) = c_0^\infty. \tag{10}$$

Notice that the structure of this limit problem is plausible, which can be seen by differentiating $R(c^k)$ and letting $k \to \infty$, assuming that $\frac{d}{dt} R(c_k(t)) \to 0$ for $t > 0$.

Theorem 2. *Suppose that the stoichiometric vectors $\alpha_j, \beta_j \in \mathbb{N}_0^n$ for $j = 1, \dots, m$ are such that $\{v_1, \dots, v_m\}$ with $v_j = \beta_j - \alpha_j$ is a linearly independent subset of $\mathbb{R}^n$. Let $k_j, \kappa_j > 0$, rate functions be given by mass-action kinetics, i.e. $r_j(c) = k_j(c^{\alpha_j} - \kappa_j c^{\beta_j})$ for $j = 1, \dots, m$, initial composition $c_0 \geqslant 0$ and $f : \mathbb{R}^n_+ \to \mathbb{R}^n$ satisfy* (8) and (9). Then

(a) *Initial value problem* (7) *has a unique global solution $c^k(\cdot)$ for every $k \geqslant 0$. This solution is strictly positive on $\mathbb{R}_+$.*
(b) *The limiting equation* (10) *has a unique global solution $c^\infty(\cdot)$. This solution is strictly positive and remains in the manifold $\mathcal{M} = \{c \geqslant 0 \colon R(c) = 0\}$. If F_∞ denotes the right-hand side in* (10), *then $F_\infty(c) = (I - P(c))f(c)$ on $\mathcal{M}$, where*

$$P(c) = N[N^T C^{-1} N]^{-1} N^T C^{-1} \quad \textit{with } C = \operatorname{diag}(c_1, \dots, c_n)$$

is the projection onto S along $CS^\perp$.
(c) *$c^k(t) \to c^\infty(t)$ as $k \to \infty$ uniformly on compact subsets of $(0, \infty)$, where the initial value c_0^∞ in* (10) *is given as the unique strictly positive equilibrium in the stoichiometric class $c_0 + S$.*

Proof. (a) Notice first that the fast reaction part $N\Lambda R(c)$ in (7) is quasi-positive by step 2 of the proof of Theorem 1. Hence the full right-hand side has this property and is locally Lipschitz continuous, which implies local existence of a unique nonnegative solution $c(\cdot) = c^k(\cdot; c_0)$ by Lemma 1. Let $[0, T)$ be its maximal interval of existence and $\varphi(t) := \langle e, c(t) \rangle$ with e from (9). Evidently

$$\dot{\varphi} = \langle e, f(c) \rangle \leqslant a\left(1 + \sum_{i=1}^{n} c_i\right) \leqslant \rho a(1+\varphi) \text{ on } [0,T)$$
$$\text{with } \rho = \max\{1, 1/e_1, \dots, 1/e_n\},$$

hence

$$|c(t)|_1 \leqslant \rho\varphi(t) \leqslant \psi(t) := \rho(1 + \langle e, c_0 \rangle)e^{\rho a t} \quad \text{on } [0,T) \tag{11}$$

due to Gronwall's Lemma and therefore $T = \infty$. It remains to show $c(t) \gg 0$ on $[0,\tau]$ for arbitrary $\tau > 0$. Since the right-hand side $F(c) = f(c) + kN\Lambda R(c)$ in (8) is locally Lipschitz, it is Lipschitz of some constant L_k on the compact set $\{c \in \mathbb{R}^n_+ : |c|_1 \leqslant \psi(\tau)\}$. Together with quasi-positivity of F this yields $F(c) \geqslant -L_k c$ for such c, hence $c_i(t) \geqslant c_{0,i}e^{-L_k t} > 0$ on $[0,\tau]$.

Consequently, initial value problem (7) has a unique global solution which stays strictly positive and satisfies (11) on all of $\mathbb{R}_+$.

(b) To prove the next part let us first show that the right-hand side F_∞ in (10) is well defined on the manifold $\mathcal{M}$. Consider a fixed $c \in \mathcal{M}$, i.e. $c \gg 0$ and $c^{\nu_j} = 1/\kappa_j$ for $j = 1, \dots, m$. Then

$$\frac{\partial R_j}{\partial c_k}(c) = \frac{\alpha_{j,k}}{c_k} c^{\alpha_j} - \kappa_j \frac{\beta_{j,k}}{c_k} c^{\beta_j} = -\frac{\nu_{j,k}}{c_k} c^{\alpha_j},$$

hence

$$R'(c) = -DN^T C^{-1} \text{ for } c \in \mathcal{M} \text{ with } D = \mathrm{diag}(c^{\alpha_1}, \dots, c^{\alpha_m}), C = \mathrm{diag}(c_1, \dots, c_n). \tag{12}$$

Therefore $R'(c)N = -DN^T C^{-1} N$ is negative definite, in particular invertible. Since $R'(c)N$ depends locally Lipschitz continuous on $c \in \mathcal{M}$, the inverse also has this property. Hence $F_\infty(c)$ is well defined and locally Lipschitz continuous on $\mathcal{M}$. Moreover, $F_\infty(c)$ has the representation mentioned in (b), and is tangent to $\mathcal{M}$ due to $R'(c)F_\infty(c) = 0$. As a consequence, the limiting equation (10) has a unique local solution $c^\infty(\cdot)$ by Lemma 1. This solution satisfies $|c^\infty(t)|_1 \leqslant \psi(t)$ on its maximal interval of existence, where ψ is given in (11); notice that $\langle e, F_\infty(c) \rangle \leqslant a(1 + |c|_1)$ on $\mathcal{M}$ with e from (9). Therefore $c^\infty(\cdot)$ exists globally if it stays strictly positive.

Assume, on the contrary, that there is $T > 0$ such that $c(t) \gg 0$ on $[0,T)$ and $\underline{\lim}_{t \nearrow T} c_i(t) = 0$ for some i. We claim that there are $\delta, \mu > 0$ such that $c(t) = c_0^\infty \cdot e^{x(t)}$ with $x(t) \in K_{\delta,\mu}$, where

$$K_{\delta,\mu} = \{x \in S^\perp : x_i \leqslant \mu \text{ for } i = 1, \dots, m, \langle e^x, y \rangle \geqslant \delta$$
$$\text{for all } y \in S^\perp \cap \mathbb{R}^n_+, |y|_1 = 1\}. \tag{13}$$

If this holds we obviously arrive at a contradiction in case $K_{\delta,\mu}$ is bounded.

Of course $c(t) = c_0^\infty \cdot e^{x(t)}$ is valid with some function $x : [0, T) \to S^\perp$ by Theorem 1(a), since $R(c(t)) = 0$ on $[0, T)$. Moreover $c(t) \in [0, M]^n$ with $M = \psi(T)$ by the estimate given in (11), hence $x_i(t) \leqslant \mu$ on $[0, T)$ for $i = 1, \dots, m$ with some $\mu > 0$. Let L be a Lipschitz constant for f on $[0, M]^n$, and recall that this implies $f(c) \geqslant -Lc$ on $[0, M]^n$ due to quasi-positivity of f. Fix $y \in S^\perp \cap \mathbb{R}^n_+$ with $|y|_1 = 1$. Then

$$\frac{d}{dt} \langle c(t), y \rangle = \langle f(c(t)), y \rangle \geqslant -L \langle c(t), y \rangle \quad \text{on } [0, T),$$

hence

$$\langle c(t), y \rangle = \langle c_0^\infty \cdot e^{x(t)}, y \rangle \geqslant \eta e^{-Lt} \text{ on } [0, T) \text{ with } \eta = \frac{1}{n} \min_i c_{0,i}^\infty.$$

This yields $\langle e^{x(t)}, y \rangle \geqslant \delta$ with $\delta = \eta e^{-LT} / \max_i c_{0,i}^\infty > 0$ and therefore $x(t) \in K_{\delta,\mu}$ on $[0, T)$.

It remains to show that $K_{\delta,\mu}$ is bounded. If not there is $(x^k) \subset K_{\delta,\mu}$ such that $|x^k|_1 \to \infty$, and w.l.o.g. $x_i^k \to -\infty$ if $i \in I$ and (x_i^k) is bounded if $i \notin I$ with some $\emptyset \neq I \subset \{1, \dots, n\}$. We may also assume $z^k := x^k / |x^k|_1 \to z$. Evidently $z \in S^\perp$ with $|z|_1 = 1$ and $z_i \leqslant 0$ if $i \in I$, $z_i = 0$ if $i \notin I$. Hence $y := -z$ is "admissible" in the definition of $K_{\delta,\mu}$ which leads to the contradiction

$$0 < \delta \leqslant \langle e^{x^k}, y \rangle = \sum_{i \in I} y_i e^{x_i^k} \leqslant \sum_{i \in I} e^{x_i^k} \to 0.$$

(c) Below, the following facts will be used frequently. Let $J = [0, T]$ with $T > 0$, $c(\cdot)$ be a solution of (7) for arbitrary $k \geqslant 0$ and $c^*(t)$ denote the unique strictly positive equilibrium of (2) in the class $c(t) + S$. Then there are $K, L, M, M^*, \eta > 0$, all depending on T but independent of $k \geqslant 0$, such that

$$\begin{aligned} &0 < c_i(t) \leqslant M, \quad 0 < \eta \leqslant c_i^*(t) \leqslant M^* \text{ on } J \text{ for } i = 1, \dots, n, \\ &|f(c)|_\infty \leqslant K \text{ and } f \text{ is Lipschitz of constant } L \text{ on } [0, M]^n. \end{aligned} \tag{14}$$

The bounds for $c^*(t)$ need further explanation, while the other facts are direct consequences of parts (a) and (b) of this proof. Theorem 1(c) yields $c^*(t) = \lim_{\tau \to \infty} z(\tau)$ where

$$\dot{z}(\tau) = N \Lambda R(z(\tau)) \quad \text{on } \mathbb{R}_+, \quad z(0) = c(t).$$

Fix $\bar{c} \geqslant 0$ with $R(\bar{c}) = 0$ and let V be given by (4). Now observe first that $h(x) = x \ln(x/\bar{x}) - (x - \bar{x})$ with $\bar{x} > 0$ has $h''(x) = 1/x$ for $x > 0$. Hence

$$h(x) = \int_{\bar{x}}^x \int_{\bar{x}}^s \frac{1}{r} \, dr \, ds \geqslant \frac{(x - \bar{x})^2}{2x} \geqslant \frac{x}{2} - \bar{x} \quad \text{for } x \geqslant \bar{x},$$

and therefore $x \leqslant 2(\bar{x} + h(x))$ for all $x \geqslant 0$ which yields

$$|c|_1 = \sum_{i=1}^{n} c_i \leqslant 2(|\bar{c}|_1 + V(c)) \quad \text{for all } c \in \mathbb{R}_+^n.$$

Consequently,

$$|c^*(t)|_1 \leqslant 2(|\bar{c}|_1 + V(c^*(t))) \leqslant 2(|\bar{c}|_1 + V(c(t))),$$

since V is a Lyapunov function for (2). This yields upper bounds on the $c_i^*(t)$. Having upper bounds, the same arguments as given below (13) show that $c^*(t) = c_0^\infty \cdot e^{x(t)}$ with $x(t) \in K_{\delta,\mu}$ on J, where $\delta, \mu > 0$ are independent of $k \geqslant 0$. Since $K_{\delta,\mu}$ from (13) is bounded, this also yields strictly positive lower bounds for the $c_i^*(t)$.

In the subsequent steps we omit the argument t whenever this is reasonable.

(i) Consider $V(c, \phi(c))$ where $V : (0, \infty)^n \times (0, \infty)^n \to \mathbb{R}_+$ is given by

$$V(c, c^*) = \sum_{i=1}^{n} c_i \ln \frac{c_i}{c_i^*} - (c_i - c_i^*), \tag{15}$$

and $\phi(c)$ denotes the unique strictly positive equilibrium in the class $c + S$ for $c \geqslant 0$; recall that $\phi : (0, \infty)^n \to (0, \infty)^n$ is well defined by Theorem 1(a), and

$$\phi(c) = c^* \text{ iff } R(c^*) = 0 \quad \text{and} \quad Ec^* = Ec.$$

We claim that for every $T > 0$ there exist $\omega_T > 0$ and $M_T > 0$ such that

$$\frac{d}{dt} V(c^k(t), \phi(c^k(t))) \leqslant M_T - \omega_T k \sum_{j=1}^{m} \lambda_j R_j(c^k(t))^2 \text{ on } [0, T] \quad \text{for all } k \geqslant 0, \tag{16}$$

where $c^k(\cdot)$ is the solution of (7).

To establish (16), fix $k \geqslant 0$ and let $c(\cdot) = c^k(\cdot)$ as well as $c^*(\cdot) = \phi(c^k(\cdot))$. Evidently $c^*(\cdot)$ is differentiable if ϕ has this property. Since ϕ is implicitly defined by $F(c, c^*) = 0$ with $F(c, c^*) = (R(c^*), E(c^* - c))$, differentiability of ϕ follows by the implicit function theorem in case $\det(\frac{\partial F}{\partial c^*}(c, c^*)) \neq 0$ if $F(c, c^*) = 0$. Let $x \in \ker(\frac{\partial F}{\partial c^*}(c, c^*))$ for such c, c^*. This implies $R'(c^*)x = 0$ and $Ex = 0$, hence $\frac{x}{c^*} \in S^\perp$ by (12) and $x \in S$. Therefore $\langle \frac{x}{c^*}, x \rangle = 0$, hence $x = 0$. Consequently, to establish (16) we have to obtain appropriate bounds for

$$\frac{d}{dt} V(c, c^*) = \langle \ln \frac{c}{c^*}, f(c) \rangle + k \langle \ln \frac{c}{c^*}, N\Lambda R(c) \rangle + \langle \mathbf{1} - \frac{c}{c^*}, \dot{c}^* \rangle \tag{17}$$

with $\mathbf{1} = (1, \ldots, 1)$. The first term on the right is bounded due to (14) combined with

$$f_i(c) \ln c_i \leqslant -Lc_i \ln c_i \leqslant L/e \quad \text{if } 0 < c_i \leqslant 1. \tag{18}$$

To obtain an estimate for the last term, notice that $R(c^*(t)) \equiv 0$ implies $R'(c^*)\dot{c}^* = 0$, hence $\dot{c}^*/c^* \in S^\perp$ by (12). On the other hand $E\dot{c}^* = E\dot{c} = Ef(c)$, i.e. $\dot{c}^* - f(c) \in S$ and therefore $\langle \dot{c}^*/c^*, \dot{c}^* - f(c) \rangle = 0$. By Cauchy–Schwarz, this yields

$$\sum_{i=1}^{n} \frac{(\dot{c}_i^*)^2}{c_i^*} \leqslant \sum_{i=1}^{n} \frac{f_i(c)^2}{c_i^*}, \text{ hence } |\dot{c}^*|_2 \leqslant \sqrt{M^*/\eta}\ |f(c)|_2.$$

By means of (14) it follows that $|\langle \mathbf{1} - \frac{c}{c^*}, \dot{c}^* \rangle|$ is bounded. Hence there is $M_T > 0$ such that

$$\frac{d}{dt} V(c, c^*) \leqslant M_T + k\left\langle \ln \frac{c}{c^*}, N\Lambda R(c) \right\rangle,$$

and then (16) follows by means of (6) and (14); recall that k_j in (6) corresponds to $k\lambda_j$.

(ii) Consider $W : (0, \infty)^n \to \mathbb{R}_+$ defined by

$$W(c) = |D(c)^{-1/2} \Lambda^{1/2} R(c)|_2 \quad \text{with } D(c) = \operatorname{diag}(c^{\alpha_1}, \ldots, c^{\alpha_m}).$$

Suppose that $c_i^k(t) \geqslant \gamma > 0$ on $[0, a]$ for $i = 1, \ldots, n$ and all $k \geqslant 0$. We claim that, in this situation, there are constants $K_1, K_2, \sigma > 0$ and $k_0 > 0$ such that

$$W(c^k(t)) \leqslant W(c_0) K_1 e^{-\sigma k t} + \frac{K_2}{\sigma k} \text{ on } [0, a] \text{ for all } k \geqslant k_0, \tag{19}$$

where $c^k(\cdot)$ is the solution of (7). Let $\varphi(t) = W(c^k(t))$ on $[0, a]$. Then (19) is valid if the differential inequality

$$\varphi' \leqslant L_1 - k(2\sigma - L_2\varphi)\varphi \text{ a.e. on } [0, a] \text{ for all } k \geqslant k_0 \tag{20}$$

holds with $L_1, L_2, \sigma > 0$ independent of k. Indeed, (20) implies

$$\varphi(t) \leqslant \varphi(0) e^{-2\sigma k t} \exp\left(kL_2 \int_0^t \varphi(\tau)\, d\tau\right) + L_1 \int_0^t e^{-2\sigma k(t-s)} \exp\left(kL_2 \int_s^t \varphi(\tau)\, d\tau\right) ds$$

by Gronwall's lemma, and

$$kL_2 \int_s^t \varphi(\tau)\, d\tau \leqslant kL_2 \sqrt{t-s} \left(\int_s^t \varphi(\tau)^2\, d\tau\right)^{1/2} \leqslant k\sigma(t-s) + k\frac{L_2^2}{4\sigma} \int_s^t \varphi(\tau)^2\, d\tau.$$

By (14) there is $\rho > 0$ such that $\varphi(\tau)^2 = \langle D(c^k)^{-1} \Lambda R(c^k), R(c^k) \rangle \leqslant \rho \sum_{j=1}^m \lambda_j R_j(c^k)^2$, hence the integrated version of (16) implies

$$k\frac{L_2^2}{4\sigma} \int_s^t \varphi(\tau)^2\, d\tau \leqslant \rho \frac{L_2^2}{4\sigma} \int_s^t k \sum_{j=1}^m \lambda_j R_j(c^k(\tau))^2\, d\tau \leqslant M_{a,\gamma} \quad \text{for } 0 \leqslant s \leqslant t \leqslant a,$$

with some $M_{a,\gamma}$ independent of $k\geqslant 0$. Consequently,

$$\varphi(t)\leqslant\varphi(0)e^{M_{a,\gamma}}e^{-\sigma kt}+L_1e^{M_{a,\gamma}}\int_0^t e^{-\sigma ks}\,ds,$$

hence (19) is valid with $K_1=M_{a,\gamma}$ and $K_2=L_1e^{M_{a,\gamma}}$.

It remains to establish (20), where we consider $\Psi(c)=\frac{1}{2}W(c)^2=\frac{1}{2}\langle D(c)^{-1}\Lambda R(c),R(c)\rangle$ to keep the computations shorter. Elementary calculations show that

$$\nabla\Psi(c)=-\frac{1}{2}C^{-1}A^TD(c)^{-1}\Lambda R(c)^2+R'(c)^TD(c)^{-1}\Lambda R(c)$$

with $C=\mathrm{diag}(c_1,\dots,c_n)$ and $A=(\alpha_{j,k})$; notice that $\frac{\partial c^{\alpha_j}}{\partial c_k}=c^{\alpha_j}\alpha_{j,k}\frac{1}{c_k}$ and recall that $R(c)^2$ is short for $(R_1(c)^2,\dots,R_m(c)^2)$. Insertion of $\dot c=f(c)+kN\Lambda R(c)$ into $\langle\nabla\Psi(c),\dot c\rangle$ leads to four different terms that are estimated below; recall that we only need estimates that are valid for $c\in[\gamma,M]^n$. For the first term we obtain

$$-\frac{1}{2}\langle C^{-1}A^TD(c)^{-1}\Lambda R(c)^2,f(c)\rangle\leqslant|\frac{1}{2}D(c)^{-1}\Lambda R(c)^2|_1\ |AC^{-1}f(c)|_\infty\leqslant l_1\Psi(c),$$

while for the second one we have

$$\begin{aligned}-\frac{1}{2}\langle C^{-1}A^TD(c)^{-1}\Lambda R(c)^2,kN\Lambda R(c)\rangle&\leqslant k|\frac{1}{2}D(c)^{-1}\Lambda R(c)^2|_1\ |AC^{-1}N\Lambda R(c)|_\infty\\&\leqslant k\Psi(c)||AC^{-1}ND(c)^{1/2}\Lambda^{1/2}||\cdot|D(c)^{-1/2}\Lambda^{1/2}R(c)|_\infty\leqslant l_2k\Psi(c)^{3/2},\end{aligned}$$

where $||\cdot||$ denotes an appropriate matrix norm. To obtain an upper bound for the third term notice that

$$\frac{\partial R_j}{\partial c_k}(c)=\frac{\alpha_{j,k}}{c_k}c^{\alpha_j}-\kappa_j\frac{\beta_{j,k}}{c_k}c^{\beta_j}=-\frac{v_{j,k}}{c_k}c^{\alpha_j}+\frac{\beta_{j,k}}{c_k}R_j(c),$$

i.e.

$$R'(c)=-D(c)N^TC^{-1}+\mathcal{R}(c)B^TC^{-1}$$

with

$$\mathcal{R}(c)=\mathrm{diag}(R_1(c),\dots,R_m(c)),\ \ B=(\beta_{j,k}).$$

Hence $R'(c)$ is bounded on $[\gamma,M]^n$ and therefore

$$\langle R'(c)^TD(c)^{-1}\Lambda R(c),f(c)\rangle=\langle D(c)^{-1/2}\Lambda^{1/2}R(c),D(c)^{-1/2}\Lambda^{1/2}R'(c)f(c)\rangle\leqslant l_3\Psi(c)^{1/2}.$$

Concerning the last term, above formula for $R'(c)$ yields

$$\langle R'(c)^T D(c)^{-1} \Lambda R(c), kN\Lambda R(c)\rangle$$
$$= -k\langle N\Lambda R(c), C^{-1}N\Lambda R(c)\rangle + k\langle \Lambda R(c)^2, D(c)^{-1}B^T C^{-1}N\Lambda R(c)\rangle.$$

Evidently,

$$\langle N\Lambda R(c), C^{-1}N\Lambda R(c)\rangle \geqslant \frac{1}{M}\langle N^T N\Lambda R(c), \Lambda R(c)\rangle \geqslant \frac{\mu}{M}|\Lambda R(c)|_2^2,$$

where $\mu > 0$ is the smallest eigenvalue of the positive definite matrix $N^T N$. Therefore

$$\langle N\Lambda R(c), C^{-1}N\Lambda R(c)\rangle \geqslant \sigma_0 \Psi(c) \quad \text{with some } \sigma_0 > 0,$$

where σ_0 only depends on γ, M.

Since the remaining part can be estimated in the same manner as the second term, we obtain

$$\langle R'(c)^T D(c)^{-1}\Lambda R(c), kN\Lambda R(c)\rangle \leqslant -k\sigma_0\Psi(c) + l_4 k\Psi(c)^{3/2}.$$

Altogether these estimates imply

$$\frac{d}{dt}\Psi(c) \leqslant l_1\Psi(c) + l_3\Psi(c)^{1/2} + k(l_2 + l_4)\Psi(c)^{3/2} - k\sigma_0\Psi(c)$$

along the solutions $c(\cdot)^k$ of (7). By means of $\frac{d}{dt}\Psi(c^k(t)) = \varphi(t)\varphi'(t)$ a.e. and $\varphi' = 0$ a.e. on $\{t \in [0,a]\colon \varphi(t) = 0\}$ it follows that

$$\varphi' \leqslant L_1 + kL_2\varphi^2 + \frac{l_1 - k\sigma_0}{2}\varphi \quad \text{a.e on } [0,a]$$

with certain $L_1, L_2 > 0$ that are independent of k. Therefore (20) holds with $\sigma = \sigma_0/8$ and $k_0 = 2l_1/\sigma_0$, say.

(iii) Let $a > 0$ and suppose that $\min_i c_i^k(t) \geqslant \gamma$ on $[0,a]$ for all large k with some $\gamma > 0$. In this situation (19) is valid, and we claim that this implies $c^k(t) \to c^\infty(t)$ as $k \to \infty$, uniformly on compact subsets of $(0,a]$. Since the solution $c^\infty(\cdot)$ of (10) is unique, it suffices to show that, given any sequence $k_l \to \infty$, there is a subsequence of (c^{k_l}) which converges to c^∞, locally uniformly on $(0,a]$. Keeping this in mind, we again write c^k instead of c^{k_l} and subsequences thereof.

By (19) and (14) there exist $L_1, L_2, \sigma > 0$ (depending on a, γ but independent of k) and $k_0 > 0$ such that

$$|R(c^k(t))|_2 \leqslant L_1 e^{-\sigma k t} + L_2/k \text{ on } [0,a] \text{ for all } k \geqslant k_0. \tag{21}$$

Hence, given $\varepsilon \in (0,a)$, $kR(c^k(t))$ is bounded on $[\varepsilon, a]$ uniformly with respect to $k \geqslant 0$. Exploitation of the differential equation (7) shows that (c^k) is relatively compact in $C([\varepsilon,a];\mathbb{R}^n)$ for all $\varepsilon \in (0,a)$. Consideration of $\varepsilon_l \searrow 0$ together with the usual diagonalization procedure yields a subsequence of (c^k), again denoted by (c^k), such that $c^k(t) \to c(t)$ locally uniformly on $(0, a]$. Since $(kR(c^k(\cdot)))$ is weakly relatively compact in $L^1([0, a]; \mathbb{R}^n)$ by (21), we may also assume $k\Lambda R(c^k) \rightharpoonup \phi$ in $L^1([0, a]; \mathbb{R}^n)$. Therefore, integration of the differential equation for c^k from s to t and $k \to \infty$ yields

$$c(t) = c(s) + \int_s^t f(c(\tau))\, d\tau + N \int_s^t \phi(\tau)\, d\tau \quad \text{for } 0 < s < t \leqslant a,$$

hence the limit $c(\cdot)$ is absolutely continuous and satisfies

$$\dot{c} = f(c) + N\phi(t) \quad \text{a.e. on } [0, a].$$

Evidently $c(\cdot)$ also satisfies $R(c(t)) = 0$ and $c(t) \in [\gamma, M]^n$ on $(0, a]$. Consequently,

$$0 = R'(c(t))\dot{c}(t) = R'(c(t))[f(c(t)) + N\phi(t)] \text{ a.e. on } [0, a],$$

which implies

$$\phi(t) = -[R'(c(t))N]^{-1} R'(c(t)) f(c(t)) \text{ a.e. on } [0, a],$$

recall from step (b) that $R'(c)N$ is invertible on $\{c \geqslant 0\colon R(c) = 0\}$. Hence $c(\cdot)$ is a solution of the differential equation in (10) and the limit $c(0+) = \lim_{t \to 0+} c(t)$ exists, since the right-hand side $F_\infty(c)$ is bounded on $[\gamma, M]^n \cap \mathscr{M}$. Moreover

$$Ec(t) = \lim_{k \to \infty} Ec^k(t) = Ec_0 + \lim_{k \to \infty} \int_0^t Ef(c^k(s))\, ds \text{ on } (0, a]$$

implies $|Ec(t) - Ec_0| \leqslant ||E||Kt$, hence $Ec(0+) = Ec_0$. Evidently, $R(c(0+)) = 0$ and therefore $c(0+)$ is the unique strictly positive equilibrium in the class $c_0 + S$, i.e. $c(0+) = c_0^\infty$. This means $c(t) = c^\infty(t)$ on $[0, a]$, hence the claim is proved.

(iv) To finish the proof of (c) let us first show that c^k converges to c^∞, locally uniformly on some small interval $(0, a]$. This holds by the previous step if there are $a, \gamma > 0$ such that $\min_i c_i^k(t) \geqslant \gamma$ on $[0, a]$ for all large $k \geqslant 0$. Let $z(\cdot)$ be the solution of

$$\dot{z} = N\Lambda R(z) \text{ on } \mathbb{R}_+, \quad z(0) = c_0.$$

By Theorem 1(c) there is $\eta > 0$ such that $z_i(t) \geqslant 2\eta$ on $\mathbb{R}_+$ for all i, and $z(t) \to \bar{c}$ as $t \to \infty$, where $\bar{c} \gg 0$ is the equilibrium in the class $c_0 + S$ (i.e. $\bar{c} = c_0^\infty$). Let V denote the Lyapunov function from (4), and $\delta \coloneqq \frac{1}{4} \min_l \bar{c}_l$. Then $V(z(t)) \searrow 0$ as $t \to \infty$ implies $V(z(T)) \leqslant \delta$ for some $T > 0$. Consider $z^k(t) = c^k(t/k)$ on $[0, T]$ and notice that z^k is the solution of

$$\dot{z}^k = \frac{1}{k} f(z^k) + N\Lambda R(z^k) \text{ on } [0, T], \quad z^k(0) = c_0.$$

Due to the continuous dependence of $z^k(\cdot)$ on the right-hand side it follows that $z^k \to z$ in $C([0, T]; \mathbb{R}^n)$, hence $\min_i z_i^k(t) \geqslant \eta$ on $[0, T]$ and $V(z^k(T)) \leqslant 2\delta$ for all large k.

This means

$$\min_i c_i^k(t) \geqslant \eta > 0 \text{ on } [0, T/k] \text{ and } V(c^k(T/k)) \leqslant 2\delta \text{ for all large } k.$$

Since $V(c)$ satisfies $\dot{V}(c) \leqslant \langle \ln(c/\bar{c}), f(c) \rangle$, the uniform bounds given in (14) together with (18) imply $\frac{d}{dt} V(c^k(t)) \leqslant M_1$ on $[0, 1]$, say, for all $k \geqslant 0$ with some $M_1 > 0$. Hence there is $a > 0$ such that $V(c^k(t)) \leqslant 3\delta$ on $[T/k, a]$ for all $k \geqslant k_0$. Therefore, by the choice of $\delta > 0$ above, any $c := c^k(t)$ with $k \geqslant k_0$ and $t \in [T/k, a]$ satisfies

$$\frac{c_i}{\bar{c}_i} \ln \frac{c_i}{\bar{c}_i} + \frac{1}{4} \leqslant \frac{c_i}{\bar{c}_i} \quad \text{for } i = 1, \ldots, n,$$

which implies $c_i^k(t) \geqslant \rho \bar{c}_i$ on $[T/k, a]$ where $\rho > 0$ is the smallest solution of $r \ln r + 1/4 = r$. Hence

$$\min_i \; c_i^k(t) \geqslant \gamma := \min\{4\delta\rho, \eta\} > 0 \text{ on } [0, a] \text{ for } k \geqslant k_0.$$

Consequently,

$$T := \sup\{a > 0 : c^k(t) \to c^\infty(t) \text{ locally uniformly on } (0, a]\} > 0$$

by step (iii), and it remains to show $T = \infty$. Assume that $T < \infty$ and let

$$\delta = \frac{1}{4} \min\{c_i^\infty(t)\colon \; t \in [0, T], i = 1, \ldots, n\} > 0.$$

Since the estimates of type (14) are valid for the fixed interval $[0, T+1]$, there is $M_2 > 0$ such that

$$\left\langle \ln \frac{c^k(t)}{\bar{c}}, f(c^k(t)) \right\rangle \leqslant M_2 \text{ on } [0, T+1] \text{ for all } k \geqslant 0 \text{ and all } \bar{c} \in [\delta, M]^n.$$

Let $0 < a < \min\{\frac{\delta}{2M_2}, 1, T\}$. Evidently $c^k(T-a) \to \bar{c} := c^\infty(T-a) \in [\delta, M]^n$. Consider V from (4) with this particular $\bar{c}$. Then

$$\frac{d}{dt} V(c^k(t)) \leqslant M_2 \text{ on } [0, T+1] \quad \text{and} \quad V(c^k(T-a)) \leqslant \delta \text{ for all } k \geqslant k_0,$$

hence $V(c^k(t)) \leqslant 2\delta$ on $[T-a, T+a]$ for all $k \geqslant k_0$. Therefore, by a repetition of the arguments given above, there is $\gamma > 0$ such that $\min_i c_i^k(t) \geqslant \gamma$ on $[0, T+a]$ for all large k. This implies $c^k(t) \to c^\infty(t)$ locally uniformly on $(0, T+a]$ by step (iii), a contradiction. Hence $T = \infty$ which ends the proof. $\square$

Remark. In Chapter 12.5 of [12] the authors study the instantaneous reaction limit for systems of chemical reactions composed of slow and fast reactions under the assumption of mass-action kinetics but without macroscopic convection. This leads to initial value problems of type (7) with f having a special structure since it corresponds solely to additional slow reactions. There the basic idea is to rewrite system (7) in terms of slow and fast variables and to apply classical singular perturbation theory, in particular Tihonov's theorem. Translated to our notation this means to apply the transformation $u = Ec$, $v = N^T c$, and to rewrite (7) in terms of u and v. If ϕ denotes the inverse transformation, this leads to

$$\begin{aligned} &\dot{u} = Ef(\phi(u, v)) \text{ on } \mathbb{R}_+, \quad u(0) = Ec_0, \\ &\varepsilon\dot{v} = \varepsilon N^T f(\phi(u, v)) + N^T N \Lambda R(\phi(u, v)) \text{ on } \mathbb{R}_+, \quad v(0) = N^T c_0 \end{aligned} \tag{22}$$

with $\varepsilon = 1/k$. Then the limit problem is given by

$$\begin{aligned} &\dot{u} = Ef(\phi(u, v)) \text{ on } \mathbb{R}_+, \quad u(0) = Ec_0, \\ &0 = R(\phi(u, v)). \end{aligned} \tag{23}$$

Theorem 12.5.1 of this reference states that (23) has a unique local solution (u^0, v^0) on some interval $(0, T)$ and that the solutions $(u^\varepsilon, v^\varepsilon)$ converge to (u^0, v^0) as $\varepsilon \to 0+$, uniformly on compact subsets of $(0, T)$. Unfortunately, a completely rigorous proof is not given. In particular, the Theorem of Tihonov, at least in the version given in [12], does not cover this situation since ε also appears on the right-hand side in (22). Furthermore, observe that (23) is an implicit formulation of the limit problem and requires knowledge of a complete set of conserved quantities, while the explicit formulation by means of (10) only involves the stoichiometric coefficients.

Let us also note that the direct proof of Theorem 2 given here yields a thorough understanding of the particular features of system (7), which is indispensable for extensions to reaction–diffusion systems; a first step in this direction is contained in [3]. Reaction diffusion systems with a single instantaneous irreversible reaction are studied in [2] with different methods; there one can also find further references concerning the irreversible case.

4. An example from catalysis

One, if not the prototype for a catalyzed reaction is given by the scheme

$$E + S \rightleftharpoons C \rightarrow E + P.$$

The particular notation is adapted to enzyme-catalyzed reactions, where the *enzyme* E reversibly reacts with another chemical species S called *substrate* to form an enzyme–substrate *complex* C. This complex irreversibly reacts into the original enzyme plus one or more *products* P. The same kind of mechanism plays a fundamental role in all areas of catalysis. More details about catalytic reactions can be found, e.g., in [5,9].

Here, the above reaction mechanism will serve to illustrate the applicability of Theorem 2 and the difference compared to the quasi-steady-state approximation. In the simplest case of an ideally mixed batch reactor, the above scheme leads to the mathematical model

$$\begin{aligned}
\dot c_E &= -k_1 c_E c_S + k_{-1} c_C + k_2 c_C && \text{on } \mathbb{R}_+, \quad c_E(0) = c_{E,0},\\
\dot c_S &= -k_1 c_E c_S + k_{-1} c_C && \text{on } \mathbb{R}_+, \quad c_S(0) = c_{S,0},\\
\dot c_C &= k_1 c_E c_S - k_{-1} c_C - k_2 c_C && \text{on } \mathbb{R}_+, \quad c_C(0) = 0,\\
\dot c_P &= k_2 c_C && \text{on } \mathbb{R}_+, \quad c_P(0) = 0.
\end{aligned} \tag{24}$$

This initial value problem is of type (7) if we let

$$c = (c_E, c_S, c_C, c_P), \quad f(c) = (k_2 c_C, 0, -k_2 c_C, k_2 c_C),$$

$$N = (-1,-1,1,0)^T, \quad R(c) = (c_E c_S - \kappa_1 c_C) \text{ with } \kappa_1 = k_{-1}/k_1.$$

Since this example contains only one reversible reaction, we may take $k = k_1$ and $\Lambda = 1$.

If the reversible reaction is fast compared to the irreversible step, then Theorem 2 says that for large k_1 the solution of (24) will be close to the solution of the limiting problem (10). In the example considered here, this limit dynamical system is given by

$$\begin{aligned}
\dot c_E^\infty &= \frac{c_E^\infty}{c_E^\infty + c_S^\infty + \kappa_1} k_2 c_C^\infty && \text{on } \mathbb{R}_+, \quad c_E^\infty(0) = c_{E,0}^\infty,\\
\dot c_S^\infty &= -\frac{c_S^\infty + \kappa_1}{c_E^\infty + c_S^\infty + \kappa_1} k_2 c_C^\infty && \text{on } \mathbb{R}_+, \quad c_S^\infty(0) = c_{S,0}^\infty,\\
\dot c_C^\infty &= -\frac{c_E^\infty}{c_E^\infty + c_S^\infty + \kappa_1} k_2 c_C^\infty && \text{on } \mathbb{R}_+, \quad c_C^\infty(0) = c_{C,0}^\infty,\\
\dot c_P^\infty &= k_2\, c_C^\infty && \text{on } \mathbb{R}_+, \quad c_P^\infty(0) = c_{P,0}^\infty.
\end{aligned}$$

Since the system contains four species and one fast reversible reaction, there are three independent conservation laws given by

$$e^1 = (1,0,1,0), \quad e^2 = (0,1,1,0), \quad e^3 = (0,0,0,1).$$

Therefore the new initial concentrations are determined by the algebraic system

$$c_{E,0}^\infty + c_{C,0}^\infty = c_{E,0}, \quad c_{S,0}^\infty + c_{C,0}^\infty = c_{S,0}, \quad c_{P,0}^\infty = 0, \quad c_{E,0}^\infty\, c_{S,0}^\infty = \kappa_1\, c_{C,0}^\infty.$$

Let us note in passing that the identities

$$c_E^\infty + c_C^\infty \equiv c_{E,0}^\infty + c_{C,0}^\infty = c_{E,0}, \quad \kappa_1 c_E^\infty + c_E^\infty c_S^\infty \equiv \kappa_1 c_{E,0}^\infty + c_{E,0}^\infty c_{S,0}^\infty = \kappa_1 c_{E,0}$$

can be used to obtain

$$c_P^\infty(t) = c_E^\infty(t) - c_{E,0}^\infty + \kappa_1 c_{E,0}\left(\frac{1}{c_{E,0}^\infty} - \frac{1}{c_E^\infty(t)}\right) \text{ on } \mathbb{R}_+,$$

and $c_E^\infty(t)$ is given by the single differential equation

$$\dot{c}_E^\infty = \frac{(c_E^\infty)^2}{(c_E^\infty)^2 + \kappa_1 c_{E,0}} k_2(c_{E,0} - c_E^\infty) \text{ on } \mathbb{R}_+, \quad c_E^\infty(0) = c_{E,0}^\infty.$$

In Figure 1 the solution of the original system is compared to the instantaneous reaction limit, where the parameters are

$$k_1 = 25,\ k_{-1} = 7.5\ (\kappa_1 = 0.3),\ k_2 = 1.0,\ c_{E,0} = 0.5,\ c_{S,0} = 1.0.$$

The shaded curves result from the quasi-steady-state approximation which is described below.

If the irreversible reaction step is fast compared to the reversible one, the above approximation is not useful. In this case the intermediate species C will not accumulate and it is therefore reasonable to assume $c_C \approx 0$. Within the quasi-steady-state approach it is in fact assumed that even $\dot{c}_C \approx 0$, i.e. that the intermediate is in steady state. This allows for elimination of c_C in (24) which yields

$$c_C(t) = \frac{c_E(t)c_S(t)}{K_M} \quad \text{with } K_M = \frac{k_{-1} + k_2}{k_1}.$$

Since the balance equation for $c_E(t)$ is no longer useful, one now exploit the conservation law $c_E(t) + c_C(t) \equiv c_{E,0}$ to eliminate c_E. This leads to the

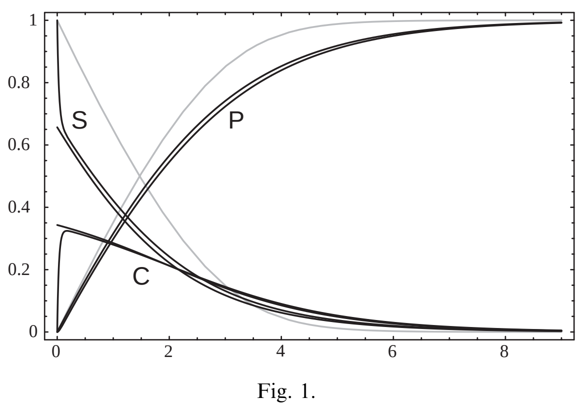

Fig. 1.

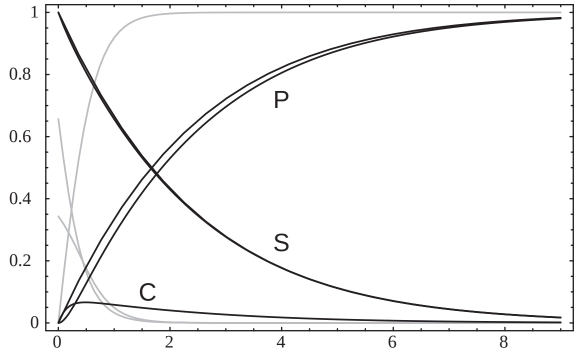

Fig. 2.

Michaelis–Menten kinetics, i.e.

$$\dot{c}_S = -k_2 c_{E,0} \frac{c_S}{K_M + c_S} \quad \text{on } \mathbb{R}_+, \quad c_S(0) = c_{S,0},$$
$$\dot{c}_P = k_2 c_{E,0} \frac{c_S}{K_M + c_S} \quad \text{on } \mathbb{R}_+, \quad c_S(0) = 0.$$

Figure 2 shows the solution of the original system compared to the quasi-steady-state approximation, where the parameters are

$$k_1 = 1,\ k_{-1} = 0.3\ (\kappa_1 = 0.3),\ k_2 = 5.0,\ c_{E,0} = 0.5,\ c_{S,0} = 1.0.$$

This time the shaded curves result from the instantaneous reaction limit.

Much more information about the quasi-steady-state approximation applied to enzyme–substrate reactions of the type considered above is provided in [10]. Additional references to related papers in the engineering literature can be found in [4,10].

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